REMARKS/ARGUMENTS

Claims 1, 3 and 4 have been amended. Claims 2, and 5-6 are canceled. Claims 1, 3, 4, and 7 are pending. Claims 8-47 are withdrawn.

Applicant has amended claims 1, 3 and 4 to more clearly define that which Applicant considers to be the invention. Specifically, Applicant has amended claim 1 to include the feature that the antibody be administered in an amount sufficient to provide the claimed effect. Support for this amendment can be found in Example 1, pages 42-43 of Applicant's specification.

Applicant amended claim 3 to delete the phrase "prevention of heart disease". In addition, Applicant amended claim 4 to clarify that the composition of claim 1 could be a component of a vaccine. Support for this amendment can be found in Applicant's specification at pages 34-37. No new matter has been added by these amendments.

Discussion of the New Matter Rejection

The Examiner rejected claims 1, 3, 4 and 7 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the specification does not appear to provide blazemarks nor direction for the term "cardiac isoforms" included in the claims. Applicant respectfully traverses this rejection.

The term "isoform" is understood by those of ordinary skill to mean that the specific amino acid sequence that is bound by the claimed antibody can vary by one or more amino acids, depending on alternative gene splicing, single nucleotide polymorphisms, etc. The antibody of the present invention is specifically directed to isoforms of the amino acid sequence of the H1-H2 domain of the Na-K ATPase in the heart (page 21 of the specification). Therefore, the term "cardiac" is meant to define the scope of the isoforms claimed as those known isoforms of the amino acid sequence of the H1-H2 domain associated with the enzyme found in the myocytes of the heart of various vertebrate species, at the time the application was filed. For example, on page 13698 of Arystakova et al., (cited by the Examiner), isoforms of the

Na-K ATPase from different species and different organs are shown. Moreover, it is known that rat has two isoforms in the heart (see, P.A. Lucchesi, et al., "Postnatal changes in Na,K-ATPase isoform expression in rat cardiac ventricle: Conservation of biphasic ouabain affinity", *J. Biol.Chem.* 266 (1991) 9327–9331; A.A. McDonough, et al., "Subcellular distribution of sodium pump isoform subunits in mammalian cardiac myocytes", *Am. J. Physiol.* 270 (1996) C1221–1227), and three isoforms in the human heart (see also, A.A. McDonough, et al., "The cardiac sodium pump: structure and function", *Basic Res. Cardiol.* 97 (Suppl. 1) (2002) I19–24; J. Wang, et al., "All human Na(+)–K(+)- ATPase alpha-subunit isoforms have a similar affinity for cardiac glycosides", *Am. J. Physiol. Cell Physiol.* 281 (2001) C1336–1343. Moreover, Applicant now submits a recently published paper in which Applicant's own data shows that both the monoclonal and polyclonal antibodies of the present invention specifically bind, and exert positive Na-K ATPase activation, in mice, dog and rat isoforms of the enzyme taken from the heart (see, for example, Applicant's specification, Examples, pages 37-42, and Kai Xu, "Dual Activity of the H1-H2 domain of the (Na+K+)-ATPase", *Biochem. Biophys. Res. Comm.* 377 (2008) 469-473) (Attached as Appendix A). Thus it is clear to one of ordinary skill in the art, that scope of the antibodies claimed by Applicant are defined as those antibodies that are generated to the peptide of SEQIDNO: 1, and those variants which are derived from the isoforms of the H1-H2 domain of the Na-K ATPase found in the cardiac myocytes of vertebrates, and more specifically, found in the cardiac myocytes of mammals, such as humans, dogs, mice, rats, pigs, etc. As such, the claim term "cardiac isoforms" is sufficiently described and supported by the specification, as well as the data published subsequently in Appendix A, and in the prior art. As such, Applicant respectfully requests withdrawal of the rejection.

Discussion of the Written Description Rejections

The Examiner rejected claims 1, 3, 4 and 7 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, the phrase "and cardiac isoforms thereof' in claim 1, lacks sufficient antecedent basis in that it is unclear if this refers to "cardiac isoforms of the sequence

RSATEEEPPNDD" or "cardiac isoforms of the α-subunit of Na-K ATPase enzyme. Applicant respectfully traverses this rejection.

In response to the rejection, Applicant submits that the antibodies claimed by Applicant are defined as those that are generated to the peptide of SEQIDNO: 1, and those variants derived from the isoforms of the H1-H2 domain of the Na-K ATPase found in the cardiac myocytes of vertebrates, and more specifically, found in the cardiac myocytes of mammals, such as humans, dogs, mice, rats, pigs, etc. The discussion in Applicant's specification regarding the number of possible amino acid variations is provided so that one or ordinary skill would understand that there could be more than one substitution of an amino acid for another in SEQIDNO: 1, yet the antibody can still bind and exert its therapeutic effect. The isoform of a protein represents any different amino acid sequence of the same protein or peptide formed due to single nucleotide polymorphisms or alternative gene splicing. To date, three isoforms of the Na-K ATPase, including α1, α2, and α3, have been found in human heart (See Kai Xu, Appendix A, page 469). These isoforms of the Na-K ATPase share the same enzymatic function with selected differences in the primary structure of the enzyme. Thus, one of ordinary skill in the art would understand that Applicant's claim would cover those variants as long as they met the limitations of specific binding and exerting its claimed effect on heart tissue. Applicant respectfully requests withdrawal of this rejection.

The Examiner rejected Claim 1, 3 and 4 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recited composition for treatment of heart failure, did not provide enablement for the term "prevention of heart failure". Applicant submits that one of ordinary skill in the art would understand that prevention of further heart failure would be expected upon treatment of a patient with the claimed invention. However, in the interest of furthering prosecution of the instant application, and in no way conceding to the Examiner's view, Applicant has amended the claim 3 to delete the term "prevention". Applicant requests withdrawal of this rejection.

Discussion of the Novelty Rejection

The Examiner again rejected claims 1, 3, 4, and 7 under 35 U.S.C. §102(b) as anticipated by Arystarkhova et al., (J Biol Chem. 1992 Jul 5;267(19):13694-701) as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886) and the instant specification at page 3, 3rd paragraph and page 43-44. The rejection is essentially identical to that made in the previous Office Action. The Examiner contends that Applicant's claims do not recite any particular structure for the claimed antibody, thus, the claimed antibody is defined by its binding specificity and its ability to increases myocyte intracellular diastolic and systolic calcium upon binding to the amino acid sequence. Applicant respectfully traverses this rejection.

The Examiner is correct that Applicant is claiming antibodies based on binding specificity and function. The Examiner contends that the VG4 antibody of Arystarkhova binds an epitope composed primarily of contiguous amino acids QAATEEEPQNDNL of pig αl Na-K ATPase, and because Arystarkhova teaches an antibody that binds to the pig αl Na-K ATPase Hl-H2 loop and "inhibits enzyme activity up to 50%", the properties of the antibody of Arystarkhova are consistent with the antibody increasing "positive inotropic activity in cardiac tissue". Therefore, according to the Examiner, if the antibodies of Arystarkhova have the same binding affinity and same function, then they anticipate Applicant's claimed composition. However, as Applicant will show, this is not the case.

In fact, Applicant's claimed antibodies surprisingly, and unexpectedly, have the opposite enzymatic function than those taught in Arystarkhova, and therefore cannot anticipate or render obvious, Applicant's claimed invention, as explained below.

First, Arystarkhova teaches that VG4 inhibits Na-K ATPase ATP hydrolysis (Fig 9). The enzyme is inhibited up to 50% when compared to control IgG (page 13699). Applicant submits that Applicant's purified monoclonal and polyclonal antibodies made to SEQIDNO: 1 according to the specification, specifically bind that portion of the H1-H2 domain and increase the activity of Na-K ATPase. Applicant invites the Examiner to review the published data by the Applicant in Appendix A. Specifically at page 471, the results show that in rat and dog isoforms of Na-K

ATPase, the antibodies of Applicant's claimed invention showed up to a 180% increase in enzyme activity over control (Fig. 2, Appendix A).

Second, Arystarkhova teaches that VG4 enhances inhibition of ATP hydrolysis by ouabain (page 13699, Fig. 10). In contrast, Applicant's antibodies inhibit or block oubain's effect on Na-K ATPase in rat and dog isoforms (Fig. 3, Appendix A).

Third, as the Examiner stated in the Office Action, it was thought that inhibition of the Na-K ATPase was what caused positive inotropic effects in heart muscle. However, Applicant has now shown that this is surprisingly not the case. Applicant's claimed antibodies actually increase Na-K ATPase activity and show a positive inotropic effect in rats. See, for example, Applicant's specification at Example 1, figures 2-6 and Appendix A, page 472 and Fig. 4. These findings are contrary to what anyone of ordinary skill in the art would have predicted for an antibody binding in the H1-H2 region of the Na-K ATPase, as claimed by Applicant.

Applicant submits that the prior art, taken as a whole, in the proper context, and in view of the latest scientific results, does not provide a reasonable scientific basis for the Examiner continue to assert that the VG4 antibody has the same structure and function as Applicant's claimed invention. Applicant has demonstrated that the Applicant's claimed invention cannot be anticipated by the VG4 antibodies of Arystarkhova, because even though the antibodies of both Arystarkhova and Applicant may have similar binding specificities, the antibodies were made using different methods, and they have completely different functional attributes. Therefore, Applicant's claimed invention cannot be assumed to be inherently taught in the prior art antibodies of Arystarkhova. As such, Applicant respectfully requests withdrawal of the rejection.

Applicant respectfully submits that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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